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Association of Digitalis Therapy With Mortality in Survivors of Acute Myocardial Infarction: Observations in the Beta-Blocker Heart Attack Trial

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The influence of digitalis therapy on survivors of acute myocardial infarction was examined in the placebo-treated patients from the Beta-Blocker Heart Attack Trial (BHAT). Two hundred fifty (13%) of the 1,921 placebo-treated patients were receiving digitalis at the time of randomization. Patients receiving digitalis differed from those not receiving digitalis in such baseline characteristics as age, prior history of heart failure, prior myocardial infarction and angina pectoris. They also experienced a higher proportion of in-hospital complications including pulmonary edema, persistent hypotension, atrial fibrillation and heart failure in addition to a greater prevalence of complex ventricular premature beats.

The total mortality rate over a mean 25 month follow-up period for digitalis-treated patients was 20.4% compared with 8.2% for patients not receiving digitalis; the odds ratio was 2.87 ($p < 0.05$). When the mortality rates were adjusted for heart failure and ventricular premature beat complexity, patients receiving digitalis again demonstrated a higher mortality rate, although the adjusted odds ratio was now lower (1.70). When the patients receiving or not receiving digitalis were compared by a multiple logistic regression analysis adjusting for 17 independent variables predictive of mortality, the use of digitalis was no longer independently predictive of total mortality (adjusted odds ratio 1.07).

These data indicate that patients receiving digitalis had more extensive cardiovascular disease and greater morbidity than patients not receiving digitalis. Their subsequent higher mortality rate was probably related to these factors rather than to digitalis therapy.

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The use of digitalis in patients with coronary heart disease in general and specifically in survivors of acute myocardial infarction is surrounded by controversy. The dispute regarding its benefits and risks in patients with heart failure began with the original reports of its use by Withering. Modern studies (1–4) have added to this controversy. Digitalis has been demonstrated to be effective in decreasing the ventricular response to atrial fibrillation and until recently it was the only positive inotropic agent available for the treatment of heart failure. Its initial salutary effect in patients was reported predominantly in the treatment of heart failure secondary to rheumatic heart disease complicated by atrial fibrillation. Since then, digitalis has been used more widely in the treatment of heart failure due to coronary heart disease. A number of investigations (7,8) have shown it to improve contractility in the failing heart.

Although clinical experience supports the efficacy of digitalis in heart failure, the drug's potential for precipitating life-threatening arrhythmia has raised questions about its lethality in patients with coronary heart disease. The poor prognosis of patients with heart failure is well established (8) and some investigators (1) have suggested that digitalis, the major means of treating heart failure, may actually contribute to the shortened survival of these patients. It also has been suggested (7) that the increased incidence of ventricular ectopic rhythm in patients with heart failure may be an expression of digitalis toxicity. However, it is difficult to separate these factors from one another because heart failure, ventricular arrhythmia and digitalis therapy are so intimately related.

Study of the patients from the Beta-Blocker Heart Attack Trial (BHAT) who received a placebo permits evaluation of the effect of the use of digitalis on mortality after myocardial infarction. Using these patients, it can be asked whether patients with myocardial infarction who were taking

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digitalis were at an increased risk of dying. It can also be asked what effect digitalis therapy had on mortality after adjusting for the presence of heart failure and other conditions. Although patients with overt heart failure with pulmonary edema were excluded from the trial population, patients who had a history of heart failure or who were successfully treated for heart failure before randomization were included in the study. The trial population represents a relatively homogeneous population from which patients with severe heart failure, for whom digitalis is the only therapeutic option, were excluded. In the patients in the trial without severe heart failure, it is possible that digitalis therapy may have been optional for other conditions, such as atrial fibrillation in addition to mild to moderate heart failure.

Methods

Study group. The Beta-Blocker Heart Attack Trial was a multicenter, placebo-controlled, double-blind trial of the long-term efficacy of propranolol given to postmyocardial infarction patients (9,10). Overall mortality was the primary end point of the trial. Men and women aged 30 to 69 years were eligible for the study and were followed up for 12 to 40 months (mean 25). Study subjects were obtained through the coronary care units of the 31 participating clinical centers. To be eligible for the trial, a patient had to have experienced an acute myocardial infarction within 5 to 21 days before randomization and have fulfilled certain inclusion and exclusion criteria specified in the protocol. Randomization and subsequent follow-up began a median of 9.3 days after hospitalization for the acute event. Of the 3,837 patients enrolled, 1,921 were randomized to the placebo group, the patients analyzed in this report. Because the trial investigators were studying propranolol, which can induce heart failure, patients judged to have severe and persistent heart failure by the investigator at each clinical center were excluded from the trial. The excluded group constituted 8% of the 16,400 patients eligible for enrollment. Thus, the trial patients, including the placebo group, were not typical of all patients who would be given digitalis after a myocardial infarction.

The patient's use of digitalis, usually as digoxin, was determined at baseline just before randomization. Although the specific reasons for the administration of digitalis were not obtained, the medical history of the patient at baseline was derived inferentially from the baseline history of heart failure and atrial fibrillation. A history of heart failure was defined as a history of heart failure before the entry myocardial infarction or during the hospitalization for the infarction or a history of shortness of breath treated with digitalis or diuretic drugs.

Electrocardiographic monitoring. Twenty-four hour ambulatory electrocardiographic (Holter) recordings were obtained before randomization in 85.4% of the patients and analyzed by previously described techniques (11). In this report, complex ventricular arrhythmia is defined as at least one ventricular premature complex pair, one ventricular tachycardia event (three or more ventricular premature ventricular complexes) or one multiform ventricular premature complex.

Mortality. Total (mean 25 month) and 4 month mortality rate are the end points of the present analysis. Vital status was not ascertained in 7 of the 1,921 patients.

Statistics. Biostatistical analyses were carried out at the Coordinating Center at the University of Texas School of Public Health. These analyses included the use of simple proportional mortality rates, the Mantel-Haenszel method for combining evidence from 2×2 tables (for the adjusted odds ratio) and Walker-Duncan multivariate logistic regressions (12).

Results

Clinical features (Table 1). Of the 1,921 placebo-treated patients, 250 (13.0%) were receiving digitalis at baseline. Patients receiving digitalis tended to be older than patients not receiving digitalis and they reported a higher frequency of previous medical conditions such as heart failure, prior myocardial infarction and angina pectoris. Proportionately more digitalis-treated patients experienced in-hospital complications such as pulmonary edema, persistent hypotension, atrial fibrillation and heart failure. Furthermore, they had a higher prevalence of complex ventricular arrhythmias.

Total mortality. The digitalis treatment group had a total mortality rate of 20.4% compared with a rate of 8.2% in patients not receiving digitalis. The odds ratio for this difference is 2.87 ($p < 0.05$). The cumulative mortality curves for those two groups are shown in Figure 1. The curves separate immediately, with a cumulative mortality rate for those receiving digitalis at baseline being consistently higher than that for patients not receiving digitalis.

Role of heart failure. Because the primary indication for digitalis is the treatment of heart failure, these data were stratified by history of the presence of heart failure (Table 2). History of heart failure increased the mortality rates in both the digitalis and nondigitalis groups, although patients receiving digitalis were still at an increased risk of dying regardless of history of heart failure. The adjusted odds ratio for this difference is 2.01, and the greatest relative difference is in the group without a history of failure. Figure 2 shows the cumulative mortality curves for patients receiving and not receiving digitalis after adjustment for the history of heart failure at baseline.

Role of ventricular arrhythmia. Because complex ventricular arrhythmia has been suggested as a cause of increased mortality in patients receiving digitalis, the data were also stratified by this characteristic (Table 2). Again, complexity of arrhythmia increased the mortality rates in

JACC Vol. 6, No. 5
November 1985:976–82

Table 1. Baseline Comparison of Patients Receiving and Not Receiving Digitalis (BHAT placebo group)

Variable	Patients Receiving Digitalis (n = 250)	Patients Not Receiving Digitalis (n = 1,671)
Sex (% men)	84.0	85.2
Age (mean)(yr)	58.5	55.0
Heart rate (mean)(beats/min)	78.2	75.4
Diastolic blood pressure (mean)(mm Hg)	71.8	72.4
Hematocrit (mean)(%)	41.4	42.0
Medical history (%)		
Heart failure	60.0	12.9
Prior myocardial infarction	23.6	13.2
Angina pectoris	43.2	35.5
Diabetes mellitus	13.2	11.1
Social history (%)		
Employed	72.0	75.5
Current smoker	51.6	57.8
Medications (%)		
Antiplatelet drugs	8.4	6.5
Diuretic drugs	45.6	13.9
Receiving a beta-blocker before entry (%)	11.6	6.1
Hospital complications (%)		
Cardiogenic shock	2.0	1.0
Persistent hypotension	11.6	6.2
Incomplete AV block	7.6	8.0
Complete AV block	4.0	2.0
Atrial fibrillation	24.5	2.9
Ventricular tachycardia	29.7	22.3
Ventricular fibrillation	10.4	4.4
Pulmonary edema	10.8	1.4
Heart failure	52.0	9.4
Other baseline characteristics (%)		
ST depression	38.0	24.2
Elevated lactic dehydrogenase	81.2	69.4
Cardiomegaly (X-ray)	49.8	32.5
Complex ventricular arrhythmia*	49.1	36.3

*Defined as at least one ventricular premature complex pair, one ventricular tachycardia event or one multiform ventricular complex. AV = atrioventricular.

both the digitalis and nondigitalis groups, although the patients receiving digitalis were still at an increased risk of dying. The adjusted odds ratio is 2.37, and the relative difference is greatest in patients with complexity. The mortality curves for the digitalis and nondigitalis groups after adjustment for the presence of ventricular premature complexity are shown in Figure 3.

When the data are stratified by both history of heart failure and complexity of arrhythmia (Table 2), the relative difference in mortality rates between the digitalis and nondigitalis groups narrows even further. Here the adjusted odds ratio is 1.70. Figure 4 shows the mortality curves after adjustment for both heart failure history and ventricular premature beat complexity.

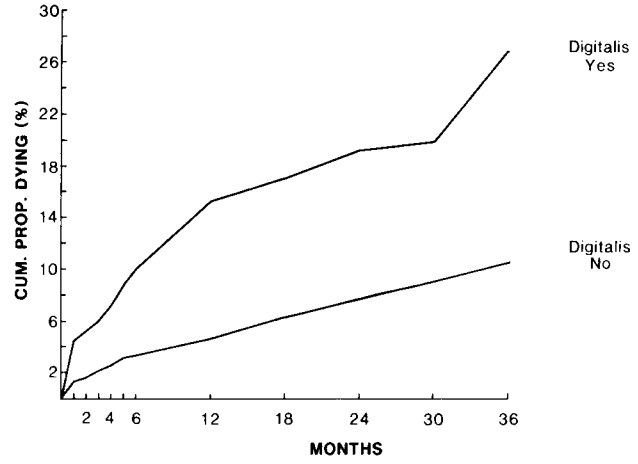


Figure 1. Cumulative (CUM.) mortality rate during 36 months of follow-up study in patients receiving or not receiving digitalis at baseline examination. PROP. = proportion.

Digitalis and mortality. In each of the previous analyses there appears to be an association between the use of digitalis and mortality, although the association weakened when the rates were adjusted for comorbidity. As noted in Table 1, the groups receiving and not receiving digitalis differed in many characteristics that could have an impact on mortality, not just heart failure and complex ventricular arrhythmia. Using the Walker-Duncan multiple logistic regression technique, adjustment was made for digitalis and 16 other independent variables known to be predictive of mortality in the placebo group (Appendix A). When these variables were considered, the use of digitalis was not independently predictive of total mortality. The adjusted odds ratio is 1.07 ($p > 0.05$).

Effects of crossover in use of digitalis. The use of digitalis may not remain constant over time. At the 3 month follow-up visit, 27.4% of the patients receiving digitalis at baseline were no longer taking it and 8.3% of those not receiving digitalis at baseline were taking it (Table 3). The use of digitalis remained reasonably constant after the 3 month visit. To examine the potential effect of their early crossover, we examined the short-term mortality rate, defined as death occurring within the first 4 months after randomization. The short-term mortality rate of patients receiving digitalis at baseline was compared with the rate for those patients not receiving digitalis, again stratified by history of heart failure and ventricular arrhythmia complexity (Table 4).

Four month mortality. This analysis indicated that the

Table 2. Overall Mortality by Baseline Digitalis Usage, History of Heart Failure and Presence of Ventricular Arrhythmia Complexity*

	Patients Receiving Digitalis		Patients Not Receiving Digitalis			
	No.	Mortality Rate (%)	No.	Mortality Rate (%)	Odds Ratio	Adjusted Odds Ratio
Overall	250	20.4	1,671	8.2	2.87	—
History of heart failure +	150	24.0	215	14.4	1.87	2.01
History of heart failure −	100	15.0	1,456	7.3	2.25	
Complexity +	106	27.4	517	13.0	2.53	2.37
Complexity −	110	11.8	907	6.0	2.12	
Heart failure +, complexity +	63	31.7	79	17.7	2.16	
Heart failure −, complexity +	43	20.9	438	12.1	1.92	
Heart failure +, complexity −	60	16.7	105	13.3	1.30	1.70
Heart failure −, complexity −	50	6.0	802	5.0	1.22	

*Defined as at least one ventricular premature complex pair, one ventricular tachycardia event or one multiform ventricular complex. Data are missing for 281 patients. + = present; − = absent.

digitalis group had an unadjusted mortality rate almost three times greater than that of the nondigitalis group (7.2 and 2.5%, respectively, odds ratio 3.01). Although patients with a history of heart failure had a higher mortality rate than patients without this history, in each group the odds ratios were similar for those receiving or not receiving digitalis. The adjusted odds ratio is 2.55. After adjustment for both heart failure history and arrhythmia complexity the odds ratio becomes 1.91. Furthermore, when the 17 variables listed in Appendix A are included in a multiple logistic regression analysis with 4 month mortality as the end point, the odds ratio decreases to 1.04.

Discussion

These analyses indicate the difficulty of separating, in a post hoc fashion, the effect of digitalis from the natural history of the clinical state it is used to treat. Patients receiving digitalis have many characteristics that place them at a greater risk of dying including, but not limited to, heart failure and complex arrhythmia. On the surface, digitalis appears to have a deleterious effect on postinfarction patients who have heart failure, with or without complex ventricular arrhythmia. However, when the numerous interactive factors bearing on cardiac mortality are controlled, the effect of digitalis on mortality rate cannot be demonstrated statistically.

Figure 2. Cumulative mortality rate during 36 months of follow-up study in patients receiving or not receiving digitalis at baseline after adjustment for the presence of heart failure at baseline. Abbreviations as in Figure 1.

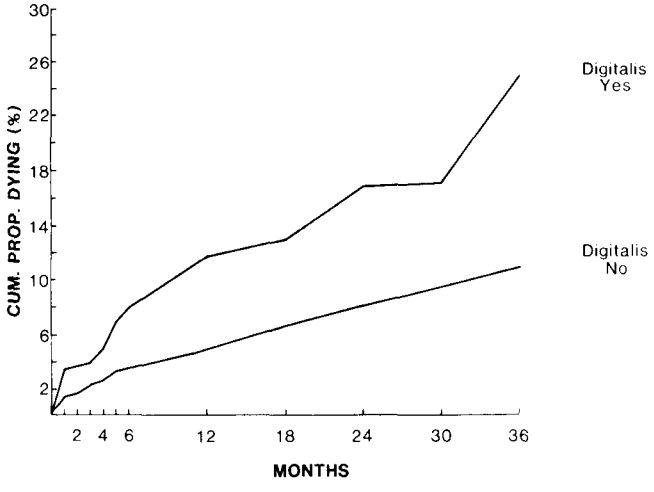
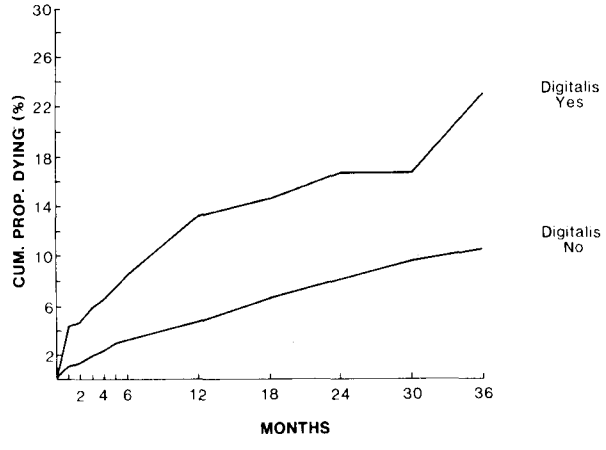


Figure 3. Cumulative mortality rate during 36 months of follow-up study in patients receiving or not receiving digitalis at baseline after adjustment for the presence of ventricular premature beat complexity. Abbreviations as in Figure 1.



JACC Vol. 6, No. 5
November 1985:976–82

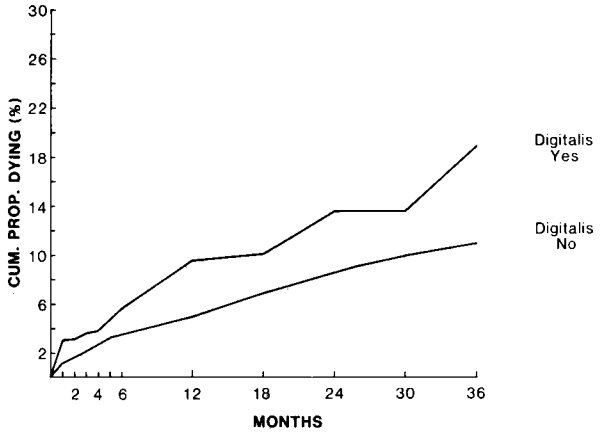


Figure 4. Cumulative mortality rate during 36 months of follow-up study in patients receiving or not receiving digitalis at baseline, after adjustment for the presence of both heart failure and ventricular premature beat complexity. Abbreviations as in Figure 1.

Table 3. Percent of Patients Discontinuing or Maintaining Digitalis Therapy at Selected Follow-Up Visits

Follow-Up Visit (mo)	Patients Receiving Digitalis at Baseline, Not Receiving It at Follow-Up	Patients Not Receiving Digitalis at Baseline, Receiving It at Follow-Up
3	27.4	8.3
6	29.3	9.5
12	33.7	11.2
24	29.8	11.3

Previous studies of role of digitalis in myocardial infarction. The experimental data suggest that there is an association between cardiac glycoside intoxication and increased susceptibility to the development of ventricular arrhythmias in infarcted hearts (13–18). Iesaka et al. (17), in an animal infarct model, demonstrated that digitalis-induced ventricular arrhythmia occurred at a lower dose in animals with infarction and that the infarcted myocardium was a preferential site of origin of digitalis-toxic arrhythmias. However, studies by Gradman et al. (15) indicated that ventricular premature complex frequency did not change with the administration of digitalis in patients with an ejection fraction of less than 50% and actually decreased in patients with a normal ejection fraction. A review of the existing clinical data suggests that myocardial contractility improves with digitalis therapy (5–7) in patients with chronic coronary hear disease. Systemic vascular resistance, however, may increase in humans as a response to intravenous administration of ouabain (19).

Moss et al. (1), studying survivors of an acute myocardial infarction, observed that the use of digitalis appeared to be related to an increased 4 month mortality rate. This increased mortality rate was confined particularly to those patients with heart failure and complex ventricular premature complexes recorded during a baseline 6 hour Holter recording. This observation was not made in our study (Table 4). Bigger et al. (5) also found an increased 1 year cardiac death rate in the digitalis-treated group even after adjusting for left ventricular failure and ventricular arrhythmia, an observation again not made here. Using data from the Coronary Artery Surgery Study, Ryan et al. (3) found a higher long-term (mean 4.5 years) mortality rate in patients receiving digitalis than in patients not receiving digitalis (18 versus 5%). When this mortality rate was adjusted for a variety of clinical, hemodynamic and angiographic variables, there was no observed effect on mortality related to digitalis therapy. Madsen et al. (2) also observed in postmyocardial

Table 4. Four Month Mortality by Baseline Digitalis Usage, History of Heart Failure and Presence of Ventricular Arrhythmia Complexity

	Patients Receiving Digitalis		Patients Not Receiving Digitalis			
	No.	Mortality Rate (%)	No.	Mortality Rate (%)	Odds Ratio	Adjusted Odds Ratio
Overall	250	7.2	1,671	2.5	3.01	—
History of heart failure +	150	9.3	215	4.7	2.11	2.02
History of heart failure −	100	4.0	1,456	2.2	1.85	
Complexity +	106	6.6	517	3.9	1.76	2.55
Complexity −	110	6.4	907	1.5	4.33	
Heart failure +, complexity +	63	6.3	79	6.3	1.00	
Heart failure −, complexity +	43	7.0	438	3.4	2.11	
Heart failure +, complexity −	60	11.7	105	2.9	4.49	1.91*
Heart failure −, complexity −	50	0.0	802	1.4	—	

*Last two strata combined as "heart failure −, complexity + or −." Ventricular complexity data are missing for 281 patients. + = present; − = absent.

infarction patients that much of the increased mortality associated with digitalis therapy was related to other clinical variables.

Comparison with previous follow-up studies. There are differences in the various populations used to study this question. Moss et al.(1) studied all patients discharged from coronary care units with heart failure and pulmonary congestion. They defined heart failure as significant rales or pitting edema, or both, and pulmonary congestion and radiographic evidence of interstitial edema. Because all patients were included in their follow-up study, the subsequent 4 month mortality rate was 11.5% in patients receiving digitalis and 3% in those not receiving digitalis. Similar 4 month mortality rates of 13 and 5%, respectively, were observed by Madsen et al. (2). In the present study, however, 8% of the patients were excluded from the trial because of severe and persistent heart failure, which is a contraindication for therapy with a beta-adrenergic blocking agent. The effect of this exclusion of higher risk patients can be seen in the lower 4 month mortality rate in our study: 7.2% in the digitalis group and 2.5% in the nondigitalis group. In general, our patients were similar to those studied by Moss et al. (1) in regard to several factors related to mortality such as frequency of previous myocardial infarction, age and presence of previous angina pectoris. Pulmonary congestion, however, was almost three times more common in the study by Moss et al. The criterion for complex ventricular arrhythmia was similar in the two studies, but the frequency of this arrhythmia was greater in our study because of the longer recording duration (24 hours compared with 6 hours in the study of Moss et al.).

Clinical implications. Given the constraints of this type of analysis, using a population such as our study patients may prove a practical approach to examining the possible deleterious effects of digitalis use. In patients with overt heart failure, the group excluded from this study, there is little alternative therapy to digitalis. The critical question is whether digitalis therapy is beneficial or deleterious in patients with mild or moderate heart failure, a group for whom the physician may have therapeutic options. Our retrospective data suggest that most of the increased mortality risk associated with digitalis therapy is due to the nature of the cardiac disease being treated. To actually test the risk of digitalis therapy in this population a randomized, placebo-controlled trial is required. Recent studies (20) on the results of withdrawal of digitalis in patients with heart failure indicate that such a trial is feasible, particularly with the development of newer methods of treating heart failure.

Appendix A

The 17 baseline variables examined were digitalis use, history of heart failure, age, employment status at the time of entry myocardial infarction, prior myocardial infarction, current smoking status, beta-blocker use before myocardial infarction, complicated myocardial infarction, antiplatelet drug use, diabetes, cardiothoracic ratio, diastolic blood pressure, diuretic drug use, ST segment depression, elevated lactic dehydrogenase, hematocrit and complexity of ventricular arrhythmia.

Appendix B

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